

AMENDMENTS TO THE CLAIMS

1-66. (canceled)

67. (Currently amended) A composition comprising a stabilized exendin-4 (1-39) comprising:

(a) a deletion of 0 to 5 amino acids at positions corresponding to position 34-38 of exendin-4; and

(b) an alpha-aspartate (Asp), ~~or a~~ beta-aspartate (isoaspartyl), or a cyclic imide residue at a position corresponding to the Asn residue at position 28 of exendin-4;

(c) optionally an oxidized methionine residue at a position corresponding to position 14 of exendin-4;

(d) optionally an oxidized tryptophan residue at a position corresponding to position 25 of exendin-4; and

(e) optionally a deamidated or hydrolyzed Gln at a position corresponding to position 13 of exendin-4.

68. (Cancelled)

69. (Currently amended) The composition of claim 67 ~~or 68~~ further comprising at least one peptide sequence Z of 4-20 amino acid residues covalently bound to the stabilized exendin; or a pharmaceutically acceptable salt or solvate thereof.

70. (Currently amended) The composition of claim ~~68~~ 67, wherein:

(a) the oxidized methionine residue is a methioninyl sulfoxide or a methioninyl sulfone; and/or

(b) the oxidized tryptophan residue comprises an oxidized 3H-indol-3-yl group; and/or

(c) the oxidized tryptophan residue is N-formylkynurenine (NFK), 3-hydroxykynurenine (3-OH-KYN), hydroxytryptophan (HTRP), or kynurenine (KYN); and/or

(d) the cyclic imide residue is an aspartimide or a glutimide.

71. (Currently amended) The composition of claim ~~67~~ 69, wherein Z comprises between about 4 to about 20 Lys amino acid units.

72. (Previously presented) The composition of claim 69, wherein Z comprises 6 Lys amino acid units.

73. (Currently amended) The composition of claim ~~67~~ 69, wherein the stabilized exendin-4 (1-39) compound and Z are bonded by a peptide bond.

74. (Currently amended) The composition of claim ~~67~~ 69, wherein Z is covalently bound to the stabilized exendin-4 (1-39) compound at the C-terminal carbonyl function.

75. (Currently amended) The composition of claim 67, wherein the stabilized exendin-4 (1-39) compound comprises a sequence selected from the group consisting of ~~any one of the following sequences:~~

des Pro³⁶[Asp²⁸]Exendin-4 (1-39),

des Pro³⁶[IsoAsp²⁸]Exendin-4 (1-39),

des Pro³⁶[D-IsoAsp²⁸]Exendin-4 (1-39),

des Pro³⁶[~~Met(0)~~¹⁴ Met(O)¹⁴, Asp²⁸]Exendin-4 (1-39),

des Pro³⁶[~~Met(0)~~¹⁴ Met(O)¹⁴, IsoAsp²⁸]Exendin-4 (1-39),

des Pro³⁶[~~Trp(02)~~²⁵ Trp(O₂)²⁵, Asp²⁸]Exendin-4 (1-39),

des Pro³⁶[~~Trp(02)~~²⁵ Trp(O₂)²⁵, IsoAsp²⁸]Exendin-4 (1-39) ~~or~~

des Pro³⁶[Met(O)¹⁴Trp(O₂)²⁵ Met(O)¹⁴, Trp(O₂)²⁵, Asp²⁸]Exendin-4 (1-39), and
 des Pro³⁶[Met(O)¹⁴Trp(O₂)²⁵ Met(O)¹⁴, Trp(O₂)²⁵, IsoAsp²⁸]Exendin-4 (1-39);

76. (Previously presented) The composition of claim 75 further comprising the following group linked to the C-terminus of the compound: -Lys₆-NH₂.

77. (Currently amended) The composition of claim 67, wherein the stabilized exendin-4 (1-39) compound comprises a sequence selected from the group consisting of any one of the following sequences:

H-(Lys)₆-des Pro³⁶[Asp²⁸]Exendin-4(1-39)-Lys₆-NH₂,
~~des Asp²⁸Pro³⁶, Pro³⁷, Pro³⁸Exendin-4(1-39)-NH₂;~~
 H-(Lys)₆-des Pro³⁶, Pro³⁷, Pro³⁸ [Asp²⁸]Exendin-4(1-39)-NH₂,
 H-Asn-(Glu)₅-des Pro³⁶, Pro³⁷, Pro³⁸ [Asp²⁸]Exendin-4(1-39)-NH₂,
 des Pro³⁶, Pro³⁷, Pro³⁸ [Asp²⁸]Exendin-4(1-39)-(Lys)₆-NH₂,
 H-(Lys)₆-des Pro³⁶, Pro³⁷, Pro³⁸ [Asp²⁸]Exendin-4(1-39)-(Lys)₆-NH₂,
 H-Asn-(Glu)₅-des Pro³⁶, Pro³⁷, Pro³⁸ [Asp²⁸]Exendin-4(1-39)-(Lys)₆-NH₂,
 H-(Lys)₆-des Pro³⁶ [Trp(O₂)²⁵, Asp²⁸]Exendin-4(1-39)-Lys₆-NH₂,
~~H-des Asp²⁸Pro³⁶, Pro³⁷, Pro³⁸[Trp(O₂)²⁵]Exendin-4(1-39)-NH₂;~~
 H-(Lys)₆-des Pro³⁶, Pro³⁷, Pro³⁸[Trp(O₂)²⁵, Asp²⁸]Exendin-4 (1-39)-NH₂,
 H-Asn-(Glu)₅-des Pro³⁶, Pro³⁷, Pro³⁸[Trp(O₂)²⁵, Asp²⁸]Exendin-4 (1-39)-NH₂,
 des Pro³⁶, Pro³⁷, Pro³⁸ [~~Trp(O₂)²⁵~~ Trp(O₂)²⁵, Asp²⁸]Exendin-4(1-39)-(Lys)₆-NH₂,
 H-(Lys)₆-des Pro³⁶, Pro³⁷, Pro³⁸ [Trp(O₂)²⁵, Asp²⁸]Exendin-4(1-39)-(Lys)₆-NH₂,
 H-Asn-(Glu)₅-des Pro³⁶, Pro³⁷, Pro³⁸ [Trp(O₂)²⁵, Asp²⁸]Exendin-4(1-39)-(Lys)₆-
 NH₂,
 H-(Lys)₆-des Pro³⁶ [Met(O)¹⁴, Asp²⁸]Exendin-4(1-39)-Lys₆-NH₂,
~~des Met(O)¹⁴ Asp²⁸Pro³⁶, Pro³⁷, Pro³⁸Exendin-4(1-39)-NH₂;~~
 H-(Lys)₆-des Pro³⁶, Pro³⁷, Pro³⁸ [Met(O)¹⁴, Asp²⁸]Exendin-4(1-39)-NH₂,

H-Asn-(Glu)₅-des Pro³⁶, Pro³⁷, Pro³⁸ [Met(O)¹⁴, Asp²⁸]Exendin-4(1-39)-NH₂,
 des Pro³⁶, Pro³⁷, Pro³⁸ [Met(O)¹⁴, Asp²⁸]Exendin-4(1-39)-(Lys)₆-NH₂,
 H-(Lys)₆-des Pro³⁶, Pro³⁷, Pro³⁸ [Met(O)¹⁴, Asp²⁸]Exendin-4(1-39)-(Lys)₆-NH₂,
 H-Asn-(Glu)₅ des Pro³⁶, Pro³⁷, Pro³⁸ [Met(O)¹⁴, Asp²⁸]Exendin-4(1-39)-(Lys)₆-
 NH₂,
 H-Lys₆-des Pro³⁶ [Met(O)¹⁴, Trp(O₂)²⁵, Asp²⁸]Exendin-4 (1-39)-Lys₆-NH₂,
~~H-des Asp²⁸Pro³⁶, Pro³⁷, Pro³⁸ [Met(O)¹⁴, Trp(O₂)²⁵]Exendin-4(1-39)-NH₂,~~
 H-(Lys)₆-des Pro³⁶, Pro³⁷, Pro³⁸ [Met(O)¹⁴, Trp(O₂)²⁵, Asp²⁸]Exendin-4(1-39)-NH₂,
 H-Asn-(Glu)₅-des Pro³⁶, Pro³⁷, Pro³⁸ [Met(O)¹⁴, Trp(O₂)²⁵, Asp²⁸]Exendin-4(1-39)-
 NH₂,
 des Pro³⁶, Pro³⁷, Pro³⁸ [Met(O)¹⁴, Trp(O₂)²⁵, Asp²⁸]Exendin-4 (1-39)-(Lys)₆-NH₂,
 H-(Lys)₆-des Pro³⁶, Pro³⁷, Pro³⁸ [Met(O)¹⁴, Trp(O₂)²⁵, Asp²⁸]Exendin-4(~~S1-39~~ 1-
39)-(Lys)₆-NH₂, and
 H-Asn-(Glu)₅-des Pro³⁶, Pro³⁷, Pro³⁸ [Met(O)¹⁴, Trp(O₂)²⁵, Asp²⁸]Exendin-4(1-39)-
 (Lys)₆-NH₂,
 or a pharmaceutically acceptable salt or solvate thereof.

78. (Previously presented) The composition of claim 67, wherein the amino acid residues have an L-configuration, a D-configuration, or the composition includes a mixture of L- and D-amino acid residues.

79. (Currently amended) A composition of any one of claims 67, ~~68, or~~ and 70-78, further comprising a pharmaceutically acceptable carrier.

80. (Previously presented) A composition of claim 69, further comprising a pharmaceutically acceptable carrier.

81. (Previously presented) The composition of claim 79, wherein the composition comprises a depot formulation, microspheres, liposomes or the composition includes a stabilized liquid formulation.

82. (Previously presented) The composition of claim 80, wherein the composition comprises a depot formulation, microspheres, liposomes or the composition includes a stabilized liquid formulation.

83. (Currently amended) The pharmaceutically acceptable composition of claim 79, wherein the composition comprises at least one stabilized exendin-4 compound, said compound comprising a sequence selected from the group consisting of the following compounds:

des Pro³⁶ [Asp²⁸]Exendin-4 (1-39),
des Pro³⁶ [IsoAsp²⁸]Exendin-4 (1-39),
~~des Pro³⁶ [Met(O)¹⁴]Exendin-4 (1-39),~~
des Pro³⁶ [Trp(O₂)²⁵]Exendin-4 (1-39),
des Pro³⁶ [Met(O)¹⁴, Asp²⁸]Exendin-4 (1-39)
des Pro³⁶ [Met(O)¹⁴, ~~IsoAsp²⁸~~ IsoAsp²⁸]Exendin-4 (1-39),
~~des Pro³⁶ [Met(O)¹⁴, Trp(O₂)²⁵]Exendin-4 (1-39),~~
des Pro³⁶ [Trp(O₂)²⁵, Asp²⁸]Exendin-4 (1-39),
des Pro³⁶ [Trp(O₂)²⁵, IsoAsp²⁸]Exendin-4 (1-39),
~~des Pro³⁶ [Met(O)¹⁴, Trp(O₂)²⁵]Exendin-4 (1-39),~~
des Pro³⁶ [Met(O)¹⁴, Trp(O₂)²⁵, Asp²⁸]Exendin-4 (1-39), and
des Pro³⁶ [Met(O)¹⁴, Trp(O₂)²⁵, IsoAsp²⁸]Exendin-4 (1-39), and.

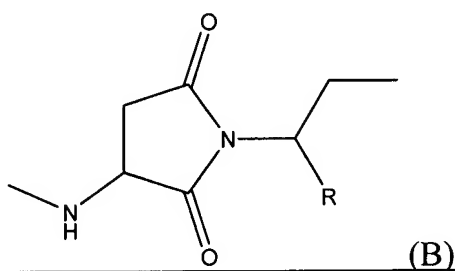
84. (Previously presented) The composition of claim 83 further comprising the following group linked to the C-terminus of the compound: -Lys₆-NH₂.

85. (Previously presented) A method of making the composition of claim 67, the method comprising at least one of the following steps:

- (a) obtaining exendin-4 (1-39) or a variant, analogue, or derivative thereof; and
- (b) incubating the exendin-4 (1-39) or the variant, analogue, or derivative thereof under conditions sufficient to introduce at least one of the following amino acids therein: an Asn residue having a deamidated side chain, an Asn residue having hydrolyzed side chain or a structural isomer of an Asp residue, wherein the Asn or Asp residue corresponds to position 28 of exendin-4.

86. (Currently amended) The method of claim 85, wherein the conditions introduce at least one of the modifications selected from the group consisting of following:

- (i) an oxidized methionine residue corresponding to position 14 of exendin-4,
- (i) an oxidized tryptophan residue corresponding to position 25 of exendin-4; and
- (iii) a deaminated or hydrolyzed Gln corresponding to position 13 of exendin-4.
- (iv) a cyclic imide having the structure B:



87. (Currently amended) The method of claim 86 further comprising the step of detecting presence or absence of at least one of amino acids ~~(i)-(iii)~~ (i)-(iv).

88. (Currently amended) The method of claim 87, further comprising the step of identifying at least one of the amino acids ~~(i)-(iii)~~ (i)-(iv) in the composition.

89. (Previously presented) The method of claim 85, wherein the conditions include contact with at least one of water, heat, light, metal, metal ions, water vapor or oxygen.

90. (Previously presented) The method of claim 89, wherein the conditions further include contact with about room temperature (25°C).

91. (Previously presented) The method of claim 90, wherein the conditions further include contact with air.

92. (Previously presented) A method for treating diabetes type 1 or type 2, insulin resistance syndrome, impaired glucose tolerance (IGT), obesity, eating disorders, hyperglycemia, metabolic disorders, and gastric disease, the method comprising administering a therapeutically effective amount of the composition of claim 67.

93. (Currently amended) A method for treating disease states associated with elevated blood glucose levels, said method comprising administering a therapeutically effective amount of the composition of claim 67-~~or 68~~.

94. (Previously presented) A method for treating disease states associated with elevated blood glucose levels, said method comprising administering a therapeutically effective amount of the composition of claim 69.

95. (Currently amended) A method for regulation of blood glucose levels, the method comprising administering a therapeutically effective amount of the composition of claim ~~67~~-~~or 68~~.

96. (Previously presented) A method for regulation of blood glucose levels, the method comprising administering a therapeutically effective amount of the composition of claim 69.

97. (Currently amended) A method for regulation of gastric emptying, the method comprising administering a therapeutically effective amount of the composition of claim ~~67~~-~~or 68~~.

98. (Previously presented) A method for regulation of gastric emptying, the method comprising administering a therapeutically effective amount of the composition of claim 69.

99. (Currently amended) A method of stimulating insulin release in a mammal comprising administering an effective insulintropic amount of the composition of claim ~~67~~-~~or 68~~.

100. (Previously presented) A method of stimulating insulin release in a mammal comprising administering an effective insulintropic amount of the composition of claim 69.

101. (Currently amended) A method for treating any one of the following conditions: diabetes type 1 or type 2, insulin resistance syndrome, impaired glucose tolerance (IGT), obesity, eating disorders, 30 hyperglycemia, metabolic disorders, and

gastric disease, disease states associated with elevated blood glucose levels, regulation of blood glucose levels, regulation of gastric emptying, stimulating insulin release, the method comprising administering to a mammal in need of such treatment, a therapeutically specific amount of the composition of claim 67 ~~or 68~~.

102. (Currently amended) A method for treating any one of the following conditions: diabetes type 1 or type 2, insulin resistance syndrome, impaired glucose tolerance (IGT), obesity, eating disorders, 30 hyperglycemia, metabolic disorders, and gastric disease, disease states associated with elevated blood glucose levels, regulation of blood glucose levels, regulation of gastric emptying, stimulating insulin release, the method comprising administering to a mammal in need of such treatment, a therapeutically specific amount of the composition of claim 69.

103. (New) The composition of claim 67, wherein said stabilized exendin-4 (1-39) comprises a cyclic imide residue at a position corresponding to the Asn residue at position 28 of exendin-4.

104. (New) The composition of claim 103, wherein said stabilized exendin-4 (1-39) comprises a sequence selected from the group consisting of:

des Pro³⁶[Cyclic imide²⁸]Exendin-4 (1-39),

des Pro³⁶[Met(O)¹⁴, Cyclic imide²⁸]Exendin-4 (1-39),

des Pro³⁶[Trp(O₂)²⁵, Cyclic imide²⁸]Exendin-4 (1-39), and

des Pro³⁶[Met(O)¹⁴, Trp(O₂)²⁵, Cyclic imide²⁸]Exendin-4 (1-39).

105. (New) The composition of claim 104 further comprising the following group linked to the C-terminus of the compound: -Lys₆-NH₂.

106. (New) The composition of claim 103, wherein said stabilized exendin-4 (1-39) comprises a sequence selected from the group consisting of:

H-(Lys)₆-des Pro³⁶ [Cyclic imide²⁸]Exendin-4(1-39)-Lys₆-NH₂,
des Pro³⁶, Pro³⁷, Pro³⁸ [Cyclic imide²⁸]Exendin-4(1-39)-NH₂,
H-(Lys)₆-des Pro³⁶, Pro³⁷, Pro³⁸ [Cyclic imide²⁸]Exendin-4(1-39) -NH₂
H-Asn-(Glu)₅-des Pro³⁶, Pro³⁷, Pro³⁸ [Cyclic imide²⁸]Exendin-4(1-39)-NH₂,
des Pro³⁶, Pro³⁷, Pro³⁸ [Cyclic imide²⁸]Exendin-4(1-39)-(Lys)₆-NH₂,
H-(Lys)₆-des Pro³⁶, Pro³⁷, Pro³⁸ [Cyclic imide²⁸]Exendin-4(1-39)-(Lys)₆-NH₂,
H-Asn-(Glu)₅- des Pro³⁶, Pro³⁷, Pro³⁸ [Cyclic imide²⁸]Exendin-4(1-39)-(Lys)₆-NH₂,
H-(Lys)₆-des Pro³⁶ [Trp(O₂)²⁵, Cyclic imide²⁸]Exendin-4(1-39)-Lys₆-NH₂,
H-(Lys)₆-des Pro³⁶, Pro³⁷, Pro³⁸ [Trp(O₂)²⁵, Cyclic imide²⁸]Exendin-4(1-39) -NH₂,
H-Asn-(Glu)₅-des Pro³⁶, Pro³⁷, Pro³⁸ [Trp(O₂)²⁵, Cyclic imide²⁸]Exendin-4(1-39)-
NH₂,
des Pro³⁶, Pro³⁷, Pro³⁸ [Trp(O₂)²⁵, Cyclic imide²⁸]Exendin-4(1-39)-(Lys)₆-NH₂,
H-(Lys)₆-des Pro³⁶, Pro³⁷, Pro³⁸ [Trp(O₂)²⁵, Cyclic imide²⁸]Exendin-4(1-39)-(Lys)₆-
NH₂, and
H-Asn-(Glu)₅-des Pro³⁶, Pro³⁷, Pro³⁸ [Trp(O₂)²⁵, Cyclic imide²⁸]Exendin-4(1-39)-
(Lys)₆-NH₂,
or a pharmaceutically acceptable salt or solvate thereof.

107. (New) The composition of claim 67, wherein said stabilized exendin-4 (1-39) comprises a sequence selected from the group consisting of:

[Asp²⁸]Exendin-4 (1-39),
[IsoAsp²⁸]Exendin-4 (1-39),
[Cyclic imide²⁸]Exendin-4 (1-39),
[Glu¹³, Asp²⁸]Exendin-4-NH₂,
[Met(O)¹⁴, Asp²⁸]Exendin-4 (1-39),

[Met(O)¹⁴, IsoAsp²⁸]Exendin-4 (1-39),
[Met(O)¹⁴, Cyclic imide²⁸]Exendin-4 (1-39),
[Trp(O₂)²⁵, Asp²⁸]Exendin-4 (1-39),
[Trp(O₂)²⁵, IsoAsp²⁸]Exendin-4 (1-39),
[Trp(O₂)²⁵, Cyclic imide²⁸]Exendin-4 (1-39),
[Met(O)¹⁴, Trp(O₂)²⁵, Asp²⁸]Exendin-4 (1-39)
[Met(O)¹⁴, Trp(O₂)²⁵, IsoAsp²⁸]Exendin-4 (1-39), and
[Met(O)¹⁴, Trp(O₂)²⁵, Cyclic imide²⁸]Exendin-4 (1-39).

108. (New) The composition of claim 67, wherein said stabilized exendin-4 (1-39) comprises [Asp²⁸]Exendin-4 (1-39) or [Glu¹³, Asp²⁸]Exendin-4-NH₂.